17 ~~22~~. (Amended) A method of immunizing a vertebrate against influenza virus, said method comprising administering to a mucosal surface of a vertebrate a DNA transcription unit comprising DNA encoding an influenza virus antigen operatively linked to a promoter region, in a physiologically acceptable carrier, [thereby eliciting a humoral or cell-mediated immune response, or both, against the antigen,] whereby the vertebrate is protected from disease caused by influenza virus.

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Remarks

Applicants' Attorney thanks the Examiner for her helpful questions and careful consideration during the personal interview on April 24, 1996.

Claims 1, 11, 19 and 22 have been amended.

Claims 1, 2, 4, 7-14, and 17-24 are pending.

Objection to Specification and Rejection of Claims under 35 U.S.C. 112, first paragraph

The Examiner objected to the Specification and rejected Claims 1, 2, 4, 7-17, 17-20, 22 and 23, stating that:

> It is the examiner's position that the specification lacks sufficient guidance and teaching to enable the broad scope of the claims. The claims are broadly drawn to a method of immunizing a vertebrate against an infectious agent comprising administering a DNA transcription unit. As an initial matter, the examiner is interpreting "immunizing" to mean making disease resistant or disease free or protecting against disease. Secondly , the claims are so broadly drawn as to include a method of immunizing against all infectious agents at issue. The infectious agents include all viruses (including HIV), all bacteria, fungi and parasites. However, the specification lacks sufficient guidance and teaching, via working examples, to enable one of skill in the art to

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make and use the antigens for a wide variety of infectious diseases.

Applicants respectfully disagree with this assessment.

The claims, as amended, pertain to methods of immunizing a vertebrate against disease, by administering a DNA transcription unit containing DNA encoding an antigen operatively linked to a promoter region.

Applicants have demonstrated that administration of a DNA transcription unit containing influenza hemagglutinin virus subtype H1 or subtype H7 is protective against disease (see the Examples). One of ordinary skill in the art, given the teachings of the Specification, would be able to generate other DNA transcription units containing other influenza hemagglutinin subtypes which would confer protective immunity. Moreover, one of ordinary skill in the art, given the teachings of the Specification, would be able to generate other DNA transcription units containing other influenza antigens that would confer protective immunity. For example, nucleoprotein (Wraith, D.C. *et al.*, *J. Gen Virol. 68*:433-440 (1987), attached as Exhibit 1) and neuraminidase (Webster, R.G. *et al.*, *Virology 164*:230-237 (1988), attached as Exhibit 2), are known to provide protective immunity in influenza. One of ordinary skill in the art, given the teachings of the Specification, would be able to generate DNA transcription units containing these antigens, which are known to confer protective immunity, and use them to protect against disease caused by influenza. Furthermore, one of ordinary skill in the art, given the teachings of the Specification, would be able to generate DNA transcription units containing other antigens that would confer protective immunity for other diseases, by utilizing antigens that are known to provide protective immunity. One of ordinary skill in the art would be able to identify antigens known to provide protective immunity

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for particular diseases, and use those antigens in the methods of the invention to protect against disease. Therefore, this rejection is improper.

Rejection of Claims under 35 U.S.C. 103

Claims 1, 2, 4, 7-14, and 17-24 have been rejected as being obvious over WO 90/11092 in view of Huylebroeck *et al.*, essentially for the reasons set forth in previous Office Actions. Each of the references is discussed below, followed by a discussion of the combination of the references.

With regard to WO 90/11092, the Examiner stated that:

> WO 90/11092 describes a method of delivering polynucleotides into the interstitial space of a tissue comprising the cell whereby the naked polynucleotide is taken up into the interior of the cell (page 6, lines 28-37). The polynucleotides may be from a variety of viral antigens and are not limited to HIV. Vaccination with nucleic acids containing a gene for an antigen can be by a variety of routes (page 37) and in pharmaceutically acceptable vehicles (pages 38-41).

WO 90/11092 describes methods of delivering RNA or DNA polynucleotides into a vertebrate cell by interstitial delivery. WO 90/11092 states that various routes of administration and pharmaceutically acceptable vehicles can be used. WO 90/11092 states that administration of polynucleotides can be used for vaccination or gene therapy. WO 90/11092 mentions use of the methods as treatment for certain diseases, including muscular dystrophy, cystic fibrosis, genetic defects of intermediary metabolism, HIV, Alzheimer's disease, liver and lung disease caused by alpha-1-antitrypsin deficiency, and cancers. WO 90/11092 also indicates that the methods can be used for controlled release of therapeutic peptides.

In its exemplification of immunization, WO 90/11092 describes mRNA vaccination of mice to produce gp120 protein of the human immunodeficiency virus (HIV). WO 90/11092 states that an antibody response was elicited in the mice. WO 90/11092 does not teach or describe actual use of any antigen other than HIV gp-120 to generate a protective response. WO 90/11092 does not describe any protective immune response.

With regard to the Huylebroeck *et al.* reference, the Examiner stated that:

> While WO 90/11092 does not describe the influenza hemagglutinin molecule, Huylebroeck describes HA as being the most important viral antigen.

Huylebroeck *et al.* describe expression of membrane-bound and a secreted form of influenza virus HA in a transient expression system based on SV40 plasmid vectors. Huylebroeck *et al.* indicate that "Influenza virus HA is considered to be the most important viral antigen connected with the frequent antigenic changes of the virus" (p. 280).

Combination of the References

In order for references to be combined, there must be some teaching or suggestion in the prior art of record supporting the combination. However, no such teaching or suggestion appears in either WO 90/11092 or in Huylebroeck *et al.* WO 90/11092 does not teach or suggest that one of ordinary skill should look to Huylebroeck *et al.*, which pertains to influenza in particular, as opposed to looking to a reference describing any other possible virus or pathogen. Furthermore, Huylebroeck *et al.* does not teach or suggest that one of ordinary skill in the art should look to WO 90/11092, describing methods of delivering nucleic acids encoding an antigen, as opposed to any other method of delivery of an antigen. Therefore, one of ordinary skill in the art would not have been motivated to

combine the teachings of WO 90/11092 with those of Huylebroeck *et al*.

Even if the teachings of WO 90/11092 are combined with those of Huylebroeck *et al*., the current invention would not have been obvious. The criterion for determination of obviousness is set forth in *In re Dow Chemical Co*., 5 USPQ2d 1529 (CAFC 1988)), as follows:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure (citations omitted).

One of ordinary skill in the art would not have had a reasonable likelihood of success, viewed in light of the prior art. One of ordinary skill in the art would not have had a reasonable expectation, given the teachings of WO 90/11092 and of Huylebroeck *et al*., that a protective response could have been achieved. WO 90/11092 describes vaccination of mice with constructs that encode a protein from the human immunodeficiency virus (HIV), which is pathogenic to humans but not to mice. Therefore, it would not have been obvious to one of ordinary skill in the art that one could protect a vertebrate against any disease.

Furthermore, immune response such as that described in WO 90/11092 is not necessarily indicative of the ability of the vaccine to protect against infection. Cytotoxic T lymphocyte response to an antigen is not necessarily indicative of protection. For example, cytotoxic T lymphocytes are not a necessary component for protective immunizations against influenza virus in the murine model (see Scherle, P.A. *et al*., *J. Immunol. 138*:212-217 (1992); and Eichelberger, M. *et al*., *J. Exp. Med. 174*:875 (1991),

attached as Exhibits 2 and 3 to the Amendment filed February 2, 1995). Furthermore, in the chicken influenza virus model, cytotoxic T lymphocyte responses have not provided protection (see Brown, D.W. *et al.*, *Avian Diseases* *36*:515-520 (Exhibit 4 to the Amendment filed February 2, 1995). Thus, it is known in the art that production of cytotoxic T cells does not necessarily correlate with protection upon challenge. Therefore, one of ordinary skill in the art would not have had a reasonable expectation of success in protecting against disease upon challenge.

In addition, one of ordinary skill in the art would have expected that microgram quantities of protein would have been necessary to obtain protective immunization (see Fields, Orthomyoxyviruses, Vol. I, pp. 1126-1127, concerning amounts of protein used in inactivated influenza virus vaccines to obtain protection; a copy of this reference was attached as Exhibit B to the Amendment filed on February 22, 1994). Only picogram levels of protein expression were achieved in WO 90/11092 (see Figure 3). One of ordinary skill in the art would not have had a reasonable expectation that such minute levels of protein expression could have achieved protective immunization.

Thus, given the teachings of WO 90/11092 and Huylebroeck *et al.*, one of ordinary skill in the art would not have had a reasonable expectation of success. Applicants have, for the first time, demonstrated the protective effect of immunization with a DNA transcription unit. Thus, the current invention would not have been obvious, given the combination of the references, as one of ordinary skill in the art would not have had a reasonable expectation of success in achieving the claimed results.

Rejection of Claims under 35 U.S.C. 112, second paragraph

The Examiner raised new grounds of rejection for Claims 1, 2, 4, 7-14, 17-24. The Examiner stated that the claims were indefinite in the recitation of "eliciting a humoral immune response, a cell-mediated immune response or both". The claims have been amended to delete this language. It does not matter whether a humoral immune response, a cell-mediated immune response, or both, is generated: as long as the vertebrate is protected from disease by administration of the DNA transcription unit, the type of immune system response generated by administration of the DNA transcription is immaterial.

Objection to Specification under 35 U.S.C. 112, first paragraph

The Examiner objected to the Specification, stating that:

> The specification lacks sufficient guidance and teachings to show that a cell-mediated immune response was generated.

As discussed above in relation to the rejection of Claims under 35 U.S.C. 112, second paragraph, it is not relevant whether a humoral immune response, a cell-mediated immune response, or both, is generated, as long as the vertebrate is protected from disease by administration of the DNA transcription unit. One of ordinary skill in the art, given the teachings of the Specification, would be able to determine whether administration of a DNA transcription unit generated a protective effect.

Rejection of Claims under 35 U.S.C. 112, first paragraph

The Examiner rejected Claims 1, 2, 4, 7-14 and 17-24 for the reasons set forth in the objection to the Specification. The claims have been amended to delete

language pertaining to the type of immune response generated by administration of the DNA transcription unit. As discussed above, the type of immune response is immaterial to the invention: the critical element is protection from disease. Therefore, this rejection is obviated.

Conclusion

In view of the amendments and the discussion presented above, Applicants respectfully submit that the claims are in condition for allowance, and request that the Examiner reconsider and withdraw all objections and rejections.

If the Examiner believes that a telephone conversation will expedite prosecution of this application, the Examiner is requested to call Applicants' Attorney at (617) 861-6240.

Respectfully submitted,

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